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(71) Applicant: VANDE WOUDE, George, F. [US/US]; 9451 Bailey Drive N.E., Ada, MI 49301 (US).

(71) Applicant and
(72) Inventor: ZHANG, Yu-Wen [CN/US]; 532 Briar Lane, N.E., Grand Rapids, MI 49503 (US).

(74) Agent: LIVNAT, Shmuel; Venable LLP, P.O. Box 34385, Washington, DC 20043-9998 (US).

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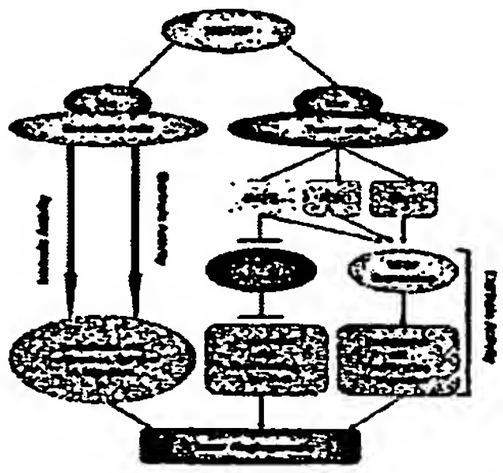
(54) Title: INHIBITION OF TUMOR ANGIOGENESIS BY COMBINATION OF THROMBOSPONDIN-1 AND INHIBITORS OF VASCULAR ENDOTHELIAL GROWTH FACTOR



(57) Abstract: Hepatocyte growth factor/scatter factor (HGF/SF), acting through the Met receptor, plays an important role in most human solid tumors and inappropriate expression of this ligand-receptor pair is often associated with poor prognosis. The molecular basis for the malignant activity imparted by signaling of HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF also induces angiogenesis, but the signaling mechanism has not been understood, nor has this activity been directly associated with HGF/SF-Met mediated tumorigenesis. HGF/SF induces expression *in vitro* of VEGF, a key agonist of tumor angiogenesis. By contrast, thrombospondin-1 (TSP-1) is a negative regulator of angiogenesis. This application discloses that, in the very same tumor cells, in addition to inducing VEGF expression, HGF/SF dramatically down regulates TSP-1 expression. TSP shut off plays an important, extrinsic role in HGF/SF-mediated tumor development, as ectopic expression of TSP-1 markedly inhibited tumor formation through the suppression of angiogenesis. While VEGF induced expression is sensitive to inhibitors of several pathways, including MAP kinase, P13 kinase and Stat3, TSP-1 shut off by HGF/SF is prevented solely by inhibiting MAP kinase activation. Thus HGF/SF is a "switch" for turning on angiogenesis. TSP-1 is a useful antagonist to tumor angiogenesis, and therefore TSP-1 and agonist peptides and mimics, as well as inducers of TSP-1, have therapeutic value when used in conjunction with inhibitors of VEGF.

WO 2005/007193 A2